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Optimum fractionation in radiotherapy—is shorter better?

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A series of multiple-fraction experiments was carried out using first-generation transplants of spontaneous mammary tumours in C3H mice. A similar series of fractionated irradiations was carried out on a normal tissue, measuring acute skin reactions in mice feet. The results will be presented as the percentage of tumours cured by a dose schedule which produced a given degree of acute skin reaction in mice.

The percentage of tumours cured, plotted against overall time of treatment for a number of fractionated schedules, shows that 9 or 10 days represent an optimum overall time for maximum cure probability at that level of acute injury to skin.

At longer overall times, results were poor because the tumours outgrew the treatment. At shorter overall times there was great variability. This can be explained on the basis of poor re-oxygenation for daily intervals but better re-oxygenation for 2-day intervals. At shorter intervals (12 hours), however, results were still good, perhaps because there was less repair in the tumours. Thus X-rays alone can produce good results, but they are quite likely not to do so, especially for rather short overall times.

When the hypoxic-cell radiosensitizer Ro-07-0582 was used with X-rays, or when cyclotron neutrons were used instead, the poor results at short overall times were all improved to the level of the best results for this degree of skin damage: the variability was eliminated. If, with these agents, short fractionation schedules become more usable, the economic advantages are obvious.

Radiosensitivity of different transplantable animal tumours and of derived cell-lines in culture

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Responses of tumours to different doses of radiation can be measured by assessment of eradication probability, volume decrease, growth delay or reproductive survival of cells. In the case of fractionated treatments, these responses are determined by many factors, namely intrinsic cellular radiosensitivity, conditions which influence this sensitivity, e.g. hypoxia, repair of sub-lethal and potentially lethal damage, and kinetics of cell proliferation and death.

To investigate the relative importance of these factors and correlations with differences between various types of tumours, a set of eight transplantable tumours and corresponding cell-culture systems has been developed from tumours which originated in different tissues. The intrinsic sensitivity to X-rays for reproductive death of cells in culture has been measured for all types of tumour; tumour-growth delay as a function of dose has been determined for five types of tumour; and reproductive death of cells in tumours after irradiation

in vivo has been determined by plating *in vitro* for two types of tumour. Results obtained for growth delay and cell reproductive death indicate that, for different tumour types, the influence of the factors mentioned varies and that interpretation of tumour responses is only possible if all factors are adequately evaluated. For instance, a rat sarcoma, R-1, shows a short growth delay of 15 days after 2000 rad of X-rays because hypoxic surviving cells respond by an increased rate of cell proliferation, whereas a rat squamous cell carcinoma, RUC-2, experiences a delay of only 10 days after 2000 rad of X-rays because it consists of cells which exhibit a high intrinsic resistance to radiation.

Tumour regression and radiation response

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The rate of tumour regression after irradiation is a poor indicator of the number of tumour cells that have been killed. It may, however, be a useful prognostic indicator of the extent of re-oxygenation during fractionated radiotherapy, which would affect the tumour radiosensitivity.

Tumours of different histological types regress at different rates after irradiation. Carcinomas often regress quickly; sarcomas often regress very slowly or not at all. This relates to the proliferation characteristics in that carcinomas have a high cell-loss factor and a constant balance between cell production and cell loss. If cell production is halted by irradiation, rapid shrinkage could result from the normal cell-loss processes. Re-oxygenation is much more effective in the three rapidly shrinking carcinomas that have been studied than in the three slowly shrinking sarcomas.

Within one histological type of tumour, the C3H mammary carcinoma, regression during fractionated treatments has been analysed in relation to the local control of each tumour at 150 days. A significant correlation was seen between shrinkage and cure rates for 3F/4 days, 9F/10 days and 15F/18 days. A weaker correlation was seen for 9F/18 days and within one week after single doses. Thus, even within one tumour type, a high rate of shrinkage may lead to an increase in the radiosensitivity of the tumour.

Importance of recruitment of non-proliferating Q into proliferating P cells for the growth of an experimental rhabdomyosarcoma before and after irradiation with X-rays

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To improve radiation and chemotherapy regimens by enhancement of the selective destruction of the clonogenic tumour cells, it is important to obtain information on the variation in the fractions of clonogenic P and Q cells in tumours before and after therapy. The cell kinetic factors involved are: the net rates of production and loss of clonogenic and non-clonogenic P and Q cells, their life-span and the rate of recruitment of Q into P cells. This latter factor and the significance of hypoxia with respect to the P or Q status of the cells have been studied for the R-1 rhabdomyosarcoma by employing the semicontinuous labelling technique and autoradiography. Animals were injected with up to seven repeated doses of ^{3}HTdR within 30 hours. Half of the labelled tumours received an acute dose of 800 rad of 300 kV X-rays 15 min before the animals were killed, in order to induce reproductive death in more than 99 per cent of the well-oxygenated cells. A slice of each tumour was fixed and used for measuring the fraction of labelled tumour cells, LI_{tumour}; from the remaining tissue of each tumour a single cell suspension was prepared for plating *in vitro*. From cultures incubated for periods of 12, 24, 48, and up to 120 h the fractions of labelled cell foci, LI_{fo}, per culture were measured.

Analysis of the variation in LI_{tumour} as a function of time and of the number of injections indicates that the rate of recruitment of Q into P cells is less than 1 per cent per hour in unirradiated tumours.